

A Potential Role of Ivacaftor in Non-Cystic Fibrosis Lung Diseases

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Introduction

Asthma and chronic obstructive lung disease (COPD) share some pathophysiologic features such as airway inflammation and mucus hypersecretion. During an episode of exacerbation, the airway smooth muscle (ASM) contracts and the mucus production increases. Mucus hypersecretion is associated with severity of the diseases and increased susceptibility to infection. Thus, management of mucosal clearance is essential for a success of asthma and COPD therapy.

Mucus production and mucosal clearance

The goblet cells and submucosal glands produce and secrete mucus. The secreted mucins consist of water (97%) and solids such as mucins, lipid, DNA (3%) [1]. There are 17 genes encoding mucins, ten of which are encoded for membrane-bound mucins and the remaining are encoded for secreted mucins [1]. The N-terminal and C-terminal of mucins contain cysteine-rich domains. These domains are covalently linked through disulfide bonds to form dimers, which further multimerized to form polymers of the mucus gel layer [2]. It is important to recognize that mucins undergo the posttranslational modification process i.e. O-glycosylation. The glycan side-chains of the mucins bind large amounts of liquid and serve as a liquid reservoir for the periciliary layer. The depth of this liquid layer is critical for the mucociliary clearance system as hydration of the mucous layer lining the airway mucosal epithelium affects its viscoelastic property. The layer of mucus moves upward from the lower to the upper respiratory track by the action of cilia. Together with cilia, it entraps and removes foreign materials, therefore the mucus layer functions as a basic defense system of the respiratory system.

Production of mucins can be upregulated by proinflammatory cytokines such as IL-9, IL-13 as well as by the activation of epidermal growth factor receptor (EGFR) [3,4]. Increased solid contents of the mucus resulting in less water content, which affects the rheology of the mucus and make it more difficult to remove from the airways. Decrease or loss of mucosal clearance allows mucus to accumulate and impede the defense mechanism. These mucus hypersecretion and mucus plugs in the respiratory tract has been shown to contribute to morbidity and mortality of chronic respiratory diseases, including severe asthma [5,6].

CFTR and CFTR mutation

Cystic fibrosis transmembrane regulator (CFTR), which also known as ATP-binding cassette C7 (ABCC7) is a membrane transporter protein. CFTR localizes to the apical membrane domain of epithelial cells lining several tissues including respiratory tract, liver, pancreas, intestine, and sweat gland. It regulates ion transport and fluid homeostasis in these organs. In the airways CFTR found to be localized throughout the lungs from the epithelia of the nose down to the proximal bronchioles [7]. The primary function of CFTR protein in the airway is to regulate rheology of mucus and thus the airway mucociliary clearance.

Like other human ABC protein, the CFTR contains two ATP-binding domains, called nucleotide-binding domains (NBDs) and two membrane-spanning domains (MSDs). These domains are organized in the arrangement of NH₂-MSD1-NBD1-R (regulatory domain)-MSD2-NBD2-COOH. To activate the CFTR, it must be phosphorylated and the binding of two ATP molecules at the interface between the two NBDs must be taken place for the channel gate to open [8]. In the airway, CFTR transport chloride ion from cytoplasm into epithelial

lining fluid bathing the respiratory epithelial". CFTR also regulates sodium reabsorption by the epithelial sodium channel. Combination of a chloride ion secretion and a reduced sodium reabsorption optimize ion compositions and the depth of airway surface liquid, enabling effective ciliary beat-driven and maintain mucociliary clearance. Some types of CFTR gene mutations affect the functionality of the protein leading to decreased chloride conductivity. Others, prevent binding and hydrolysis of ATP at the NBDs. Dysfunction of CFTR leads to a depletion of the airway surface liquid, resulting in a decreased airway mucociliary clearance.

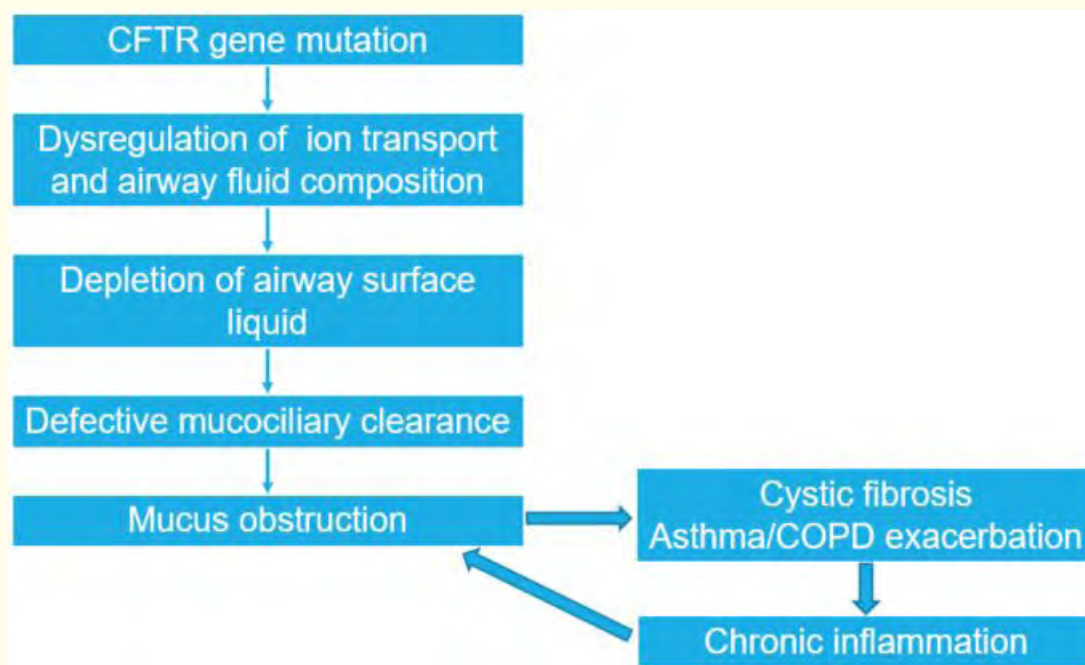


Figure 1: A potential role of CFTR in asthma/COPD exacerbation.

CFTR mutation is classified into 6 subclasses [Table 1] [9]. Deficiency or loss of function mutations of CFTR may lead to different clinical manifestations. For example the patients may have steatosis due to CFTR defect in the liver. In the airway, CFTR deficiency may cause airway obstruction, a hallmark of cystic fibrosis. Association between asthma severity and CFTR gene mutations has been reported. Amongst CFTR gene mutations, the G551D is significantly higher in detection frequency in severe asthmatic cases [10]. This finding implies that there is a subpopulation of severe asthmatic patients who may benefit from CFTR modifying therapeutic agents such as ivacaftor.

Classification	Primary characteristics
I	Defect in CFTR protein biosynthesis
II	CFTR protein misfolding, preventing trafficking to the apical surface of the cell
III	Prevent binding and hydrolysis of ATP at NBDs, dysfunction of the CFTR protein
IV	Decreased anion conduction of CFTR protein
V	Reduced number of normally functioning CFTR in the apical membrane domain
VI	Decreased CFTR membrane stability, decreasing residential time in the membrane

Table 1: Genetic classifications of CFTR genes.

NBD: Nucleotide-Binding Domain

Role of CFTR in airway mucociliary clearance

The role of CFTR in the pathophysiology of asthma and COPD is emerging. Recent development has demonstrated that, in addition to the plasma membrane, CFTR was found to be localized in the sarcoplasmic reticulum of the ASM, suggesting that CFTR may play a role in regulating ASM tone. Cook, *et al.* have demonstrated that CFTR deficiency enhances ASM constriction possible via sustaining intracellular calcium level due to a delay in calcium reuptake into the SR in combination with an increased phosphorylation of myosin light chain (MLC) [11]. A role of CFTR in non-epithelial cells remains in its infancy, nevertheless, this recent development has shed some light into an evolving physiologic function of the CFTR. Therefore, it is conceivable that a CFTR modifier such as ivacaftor may have an important role, perhaps as an adjunct therapy, in management of asthma and COPD.

Ivacaftor is a disease modifying agent for cystic fibrosis (CF). In a normal circumstance, the CFTR channel gate remain close when the catalytic site between the NBDs is not occupied by ATP. Binding of ATP to the catalytic site of between the NBDs induces conformational changes and opening of the channel gate. Ivacaftor can induce these conformational changes effective in opening the channel gate despite the absence of ATP [12]. Thus, ivacaftor causes CFTR channel opening through an ATP-independent mechanism that causes an increased chloride ion transport. The effect of ivacaftor in increasing chloride conductivity has been proved to be effective in G551D mutant CFTR proteins [13].

The role of CFTR is regulating ion transport and fluid homeostasis, and thus airway mucociliary clearance is well recognized. Mucus hypersecretion is evident in acute asthma exacerbation therefore it is conceivable that ivacaftor may benefit asthma patients through its ability in enhancing mucociliary clearance. In addition, ivacaftor decreased airway reactivity in methacholine-induced airway narrowing in porcine lung slices further support a potential role of ivacaftor in asthma therapy [11]. The pharmacologic benefit of ivacaftor on airway reactivity is supported as indicated by an improvement of force expiratory volume in 1 second (FEV1) values in persons with CF and G551D CFTR mutation [14].

Pharmacology of Ivacaftor

Ivacaftor is a CFTR modifier. It is also known as a potentiator of the CFTR protein. Ivacaftor facilitates increased chloride transport of the CFTR through a nonconventional ATP-independent mechanism.

Ivacaftor is best absorbed from the gastrointestinal tract when taken with fat containing food such as eggs, butter, and whole milk [15]. It may elevate transaminases; however, no dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). In patients with moderately impaired hepatic function (Child-Pugh Class B, score 7-9), it is recommended that the dose of ivacaftor should be reduced [15].

A potential implication of ivacaftor in non-cystic fibrosis lung diseases

Ivacaftor is indicated for the treatment of CF in patients who have class III CFTR gene mutations (Table 1) such as G551D. It has also been demonstrated that ivacaftor improved CFTR function in wild-type and in F508del mutation [16]. This flexibility of ivacaftor raises a possibility of utilizing ivacaftor in general population with asthma or COPD patients who may not have such CFTR mutations, especially for those who may have a refractory to the standard therapy. In conclusion, with its distinct mechanism of actions, namely by improving mucociliary clearance and attenuating ASM contractility, ivacaftor add-on therapy may help improve patient's lung functions, particularly in severe asthma or COPD patients, and in patients who may be resistant to the standard treatment guidelines. Apparently, to provide a true clinical benefit of ivacaftor in the treatment of non-cystic fibrosis lung diseases such as asthma and COPD, a well design clinical trials is warranted.

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